

The effect of Nipped-B-like (Nipbl) haploinsufficiency on genome-wide cohesin binding and target gene expression: modeling Cornelia de Lange syndrome.

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Authors: Daniel A Newkirk, Yen-Yun Chen, Richard Chien, Weihua Zeng, Jacob Biesinger, Ebony Flowers, Shimako Kawauchi, Rosaysela Santos, Anne L Calof, Arthur D Lander, Xiaohui Xie, Kyoko Yokomori

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Public Summary:

BACKGROUND: Cornelia de Lange syndrome (CdLS) is a multisystem developmental disorder frequently associated with heterozygous loss-of-function mutations of Nipped-B-like (NIPBL), the human homolog of *Drosophila* Nipped-B. NIPBL loads cohesin onto chromatin. Cohesin mediates sister chromatid cohesion important for mitosis but is also increasingly recognized as a regulator of gene expression. In CdLS patient cells and animal models, expression changes of multiple genes with little or no sister chromatid cohesion defect suggests that disruption of gene regulation underlies this disorder. However, the effect of NIPBL haploinsufficiency on cohesin binding, and how this relates to the clinical presentation of CdLS, has not been fully investigated. Nipbl haploinsufficiency causes CdLS-like phenotype in mice. We examined genome-wide cohesin binding and its relationship to gene expression using mouse embryonic fibroblasts (MEFs) from Nipbl^{+/−} mice that recapitulate the CdLS phenotype. **RESULTS:** We found a global decrease in cohesin binding, including at CCCTC-binding factor (CTCF) binding sites and repeat regions. Cohesin-bound genes were found to be enriched for histone H3 lysine 4 trimethylation (H3K4me3) at their promoters; were disproportionately downregulated in Nipbl mutant MEFs; and displayed evidence of reduced promoter-enhancer interaction. The results suggest that gene activation is the primary cohesin function sensitive to Nipbl reduction. Over 50% of significantly dysregulated transcripts in mutant MEFs come from cohesin target genes, including genes involved in adipogenesis that have been implicated in contributing to the CdLS phenotype. **CONCLUSIONS:** Decreased cohesin binding at the gene regions is directly linked to disease-specific expression changes. Taken together, our Nipbl haploinsufficiency model allows us to analyze the dosage effect of cohesin loading on CdLS development.

Scientific Abstract:

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